

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 9 of 15

Attorney's Docket No.: 09531-016002 / 97141

REMARKS

Claims 76-115 were pending. The Examiner rejected claims 76, 77, 79, 83-94, 96-99, 101-104, 110, 111, 114, and 115, objected to claims 78, 80-82, 95, 100, 105-109, and 113, and allowed claim 112. Applicant has canceled claims 77, 79, 83-84, 104-105, and 115 without prejudice, and has added new claim 116. Thus, claims 76, 78, 80-82, 85-103, 106-114, and 116 are pending.

Applicant has amended pages 8 and 15 of the specification to refer to the top, middle, and bottom panels of Figure 15 rather than to parts A, B, and C of the figure. Applicant has amended claims 76, 96, 98, 99, 102, and 106 to recite that the modified GLA domain comprises at least one amino acid substitution selected from the group consisting of a) substitution of a hydrophobic amino acid residue at position 33, and b) substitution of a hydrophobic amino acid residue or an aspartic acid or glutamic acid residue at position 34. Applicant also has amended claims 96 and 110 to recite that the pharmaceutical composition comprises an amount of a Factor VII or Factor VIIa polypeptide effective to increase clot formation. In addition, Applicant has amended claims 103, 110, and 111 to recite that the modified Factor VII or Factor VIIa polypeptide comprises an insertion of a tyrosine residue at position 4. Applicant has added new claim 116, which also recites a modified Factor VII or Factor VIIa polypeptide comprising an insertion of a tyrosine residue at position 4. Further, Applicant has amended the dependency of claims 78 and 80, amended claim 85 to remove the reference to position 11, and amended claim 107 to remove the reference to position 35.

Support for these amendments can be found in previous claims 77, 79, and 105, and throughout Applicant's specification. For example, the section of Applicant's specification extending from page 12, line 16 to page 13, line 13 discloses particular modifications that can be made to Factor VII or Factor VIIa polypeptides. Applicant's specification at page 21, line 29 to page 22 provides support for methods of increasing clot formation with the claimed Factor VII and Factor VIIa polypeptides. Thus, no new matter has been added.

In light of these amendments and the following remarks, Applicant respectfully requests reconsideration and allowance of claims 76, 78, 80-82, 85-103, 106-114, and 116.

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 10 of 15

Attorney's Docket No.: 09531-016002 / 97141

Specification

The Examiner objected to the specification because the Brief Description of the Drawings at page 8 of the specification refers to panels A, B, and C of Figure 15, but Figure 15 does not designate panels A, B, and C. As suggested by the Examiner, Applicant has amended the description of Figure 15 at page 8 of the specification, as well as the discussion of Figure 15 at page 45 of the specification, to refer to the top, middle, and bottom panels of Figure 15. In light of these amendments, Applicant respectfully requests withdrawal of the objection to the specification.

Priority

The Examiner stated that to claim benefit of priority to previous applications, the specification must contain a specific reference to the prior applications. Applicant has amended the cross-reference to related applications at page 1 of the specification to claim priority to PCT Application No. PCT/US00/11416.

Rejections under 35 U.S.C. § 112

The Examiner rejected claims 84, 96, 97, and 110 under 35 U.S.C. § 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter regarded as the invention. The Examiner stated that claim 84 improperly depends from itself. The Examiner further stated that claims 96, 97, and 110 are indefinite because they do not recite what effect the Factor VII or Factor VIIa is intended to have and thus the metes and bounds of "effective amount" are unclear.

Claim 84 has been canceled herein. Claims 96 and 110 have been amended to recite a pharmaceutical composition comprising a pharmaceutically acceptable carrier and an amount of a modified Factor VII or Factor VIIa polypeptide effective to increase clot formation. Thus, claims 96, 97, and 110 recite the effect the Factor VII or Factor VIIa polypeptide is intended to have, and the metes and bounds of these claims are clear.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 96, 97, and 110 under 35 U.S.C. § 112, second paragraph.

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 11 of 15

Attorney's Docket No.: 09531-016002 / 97141

Rejections under 35 U.S.C. § 102

The Examiner rejected claims 76-77, 79, 85-89, 93-94, 98, 101-104, 111, and 114-115 under 35 U.S.C. § 102(b) as being anticipated by the Cheung *et al.* reference (*Thromb. Res.* (1995) 79(2):199-206). The Examiner stated that the Cheung *et al.* reference discloses Factor VII polypeptides comprising modified GLA domains with "an asparagine substitution (a hydrophobic amino acid) at position 33 and a threonine substitution (a hydrophobic amino acid) at position 34," as well as substitutions at positions 10 and 32, and an insertion of glycine at position 4. The Examiner stated that since the Factor VII mutants of Cheung *et al.* meet all of the structural limitations of the present claims, and since the functional properties of a protein are dependent on its sequence, it would be inherent that the mutants of Cheung *et al.* would have the presently claimed functional characteristic of enhanced membrane binding affinity. The Examiner further stated that the Factor VII mutants disclosed in the Cheung *et al.* reference have additional mutations, all of which are changes from a human Factor VII amino acid to a human Factor IX amino acid at the corresponding position. The Examiner postulated that since the Factor IX GLA domain has enhanced membrane binding as compared to that of Factor VII, it would be inherent that a Factor VII protein with a GLA domain more closely resembling that of Factor IX would have enhanced membrane binding affinity. Thus, the Examiner concluded that the Factor VII mutants of Cheung *et al.* have all the structural limitations of the presently recited polypeptides, and inherently have all of the functional limitations.

Applicant respectfully disagrees. The modified Factor VII polypeptides disclosed in the Cheung *et al.* reference do not anticipate the presently claimed polypeptides. As discussed above, claims 76, 98, and 102 have been amended herein to recite that the modified GLA domain comprises at least one amino acid substitution selected from the group consisting of a) substitution of a hydrophobic amino acid residue at position 33, and b) substitution of a hydrophobic amino acid residue or an aspartic acid or glutamic acid residue at position 34. The polypeptides of the Cheung *et al.* reference do not contain such amino acid substitutions. Contrary to the Examiner's assertion, the substituted asparagine and threonine residues at positions 33 and 34 are not hydrophobic amino acids. Rather, asparagine and threonine have uncharged, polar side chains, and thus are hydrophilic. *See, e.g.,* the attached Exhibit A (Molecular Biology of the Cell 2nd edition (1989), ed. Alberts *et al.*, Garland Publishing, Inc.,

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 12 of 15

Attorney's Docket No.: 09531-016002 / 97141

New York, p. 55). Thus, none of the polypeptides disclosed in the Cheung *et al.* reference have either a) a hydrophobic amino acid residue at the position corresponding to position 33 of the presently claimed polypeptides, or b) a hydrophobic amino acid residue or an aspartic acid or glutamic acid residue at the position corresponding to position 34 of the polypeptides recited in the present claims. As such, the Cheung *et al.* reference does not anticipate present claims 76, 85-89, 93-94, 98, or 101-102.

Further, claims 103 and 111 have been amended to recite a modified Factor VII or Factor VIIa polypeptide comprising an insertion of a tyrosine residue at position 4. Although the Cheung *et al.* reference discloses insertion of a glycine at position 4 of a Factor VII polypeptide, at no point does this reference disclose a Factor VII or Factor VIIa polypeptide having a tyrosine inserted at position 4. Thus, the Cheung *et al.* reference does not anticipate present claims 103, 111, or 114.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 76, 85-89, 93-94, 98, 101-103, 111, and 114 under 35 U.S.C. § 102(b).

The Examiner rejected claims 76, 83, 96, 98, 101, and 102 under 35 U.S.C. § 102(b) as being anticipated by the Persson *et al.* reference (*FEBS Lett.* (1996) 385:241-243). The Examiner stated that the Persson *et al.* reference teaches a Factor VIIa polypeptide comprising a substitution at position 35, wherein the substituted amino acid can be, *inter alia*, valine (a hydrophobic amino acid). The Examiner stated that the Persson *et al.* reference teaches a Factor VIIa polypeptide having the same structure as the presently claimed polypeptides, and that since the function of a polypeptide is an inherent property of its structure, it appears that the mutants of Persson *et al.* would have enhanced membrane binding affinity, absent evidence to the contrary.

The Examiner's rejection is moot in view of the amendments presented herein. As discussed above, amended claims 76, 96, 98, and 102 recite that the modified GLA domain comprises at least one amino acid substitution selected from the group consisting of a) substitution of a hydrophobic amino acid residue at position 33, and b) substitution of a hydrophobic amino acid residue or an aspartic acid or glutamic acid residue at position 34. Amended claims 76, 96, 98, 101, and 102 do not refer to position 35. In contrast, the Persson *et al.* reference discloses substitutions at position 35 of Factor VIIa, but does not disclose any

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 13 of 15

Attorney's Docket No.: 09531-016002 / 97141

substitutions of the amino acids at residues 33 or 34 of Factor VIIa. Thus, the Persson *et al.* reference does not anticipate the present claims.

In light of the above, Applicant respectfully requests withdrawal of the rejection of claims 76, 96, 98, 101, and 102 under 35 U.S.C. § 102(b).

Double patenting rejection

The Examiner rejected claims 76-77, 85, 96-97, and 99 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claim 1-9 of U.S. Patent No. 6,017,882 (the '882 patent). The Examiner stated that claims 1-9 of the '882 patent differ from the present claims in that (a) they are drawn to the genus of vitamin K dependent proteins and not specifically to Factor VII or Factor VIIa, (b) they include the additional limitation that the polypeptide must increase clot formation, and (c) they fail to recite the specific amino acids to be substituted at the specific positions claimed. However, the Examiner stated that the '882 patent teaches that Factor VII is a vitamin K dependent polypeptide that can be modified to enhance membrane binding affinity, that substituting glutamine, glutamate, or aspartate at position 10; phenylalanine at position 28; and/or glutamine or aspartate at position 33 would result in the desired effect of enhancing membrane binding affinity. Thus, the Examiner concluded that it would have been obvious to select Factor VII from the vitamin K dependent proteins claimed in the '882 patent and made the specific amino acid changes claimed in the present application.

Applicant respectfully disagrees, particularly since the focus of a double patenting rejection is on the claims, not the teachings of the specification. Nevertheless, amended claims 76, 85, 96, 97, and 99 relate to Factor VII or Factor VIIa polypeptides comprising a modified GLA domain with at least one amino acid substitution selected from the group consisting of a) substitution of a hydrophobic amino acid residue at position 33, and b) substitution of a hydrophobic amino acid residue or an aspartic acid or glutamic acid residue at position 34, wherein amino acid positions of the Factor VII or Factor VIIa polypeptides are numbered according to SEQ ID NO:3. Claims 1-9 of the '882 patent relate to modified vitamin K-dependent polypeptides comprising a modified GLA domain with at least one amino acid substitution at residue 11, 12, 29, or 34. These positions correspond to positions 10, 11, 28, and

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 14 of 15

Attorney's Docket No.: 09531-016002 / 97141

33 of instant SEQ ID NO:3. None of the claims of the '882 patent recite substitutions at position 35, which would correspond to position 34 of instant SEQ ID NO:3. None of the claims of the '882 patent recite substitution of a hydrophobic amino acid residue at any of the recited positions. Thus, present claims 76, 85, 96, 97, and 99 are not obvious variants of claims 1-9 of the '882 patent. As such, a double patenting rejection is not warranted.

Objections and allowed claims

The Examiner objected to claims 78, 80-82, 95, 100, 105-109, and 113 as being dependent upon a rejected base claim. The Examiner stated that these claims would be allowable if rewritten in independent form to include all of the limitations of the base claim and any intervening claims. Given the amendments and remarks presented herein, Applicant has not presently rewritten any of these claims in independent form.

The Examiner stated that claim 112 is in condition for allowance. Specifically, the Examiner stated that there is no teaching or suggestion in the prior art of a method of increasing clot formation in a mammal comprising administering modified Factor VII or Factor VIIa comprising an insertion at position 4 according to SEQ ID NO:3. The courtesy of the Examiner in conducting a diligent search and setting forth reasons for allowability is acknowledged with appreciation. Applicant recognizes that in accordance with M.P.E.P. § 1302.14, the Examiner's statement is not intended to necessarily provide all the reasons for allowability or set forth all the details as to why this claims is allowable. In the present matter, Applicants do not concede that the Examiner's stated reasons for allowability are the only reasons for which claim 112 is in condition for allowance. For example, Applicant does not concede that all of the identified limitations are necessary to distinguish the prior art of record. Furthermore, claim 112 may be patentable for other reasons.

Applicant : Gary L. Nelsestuen
Serial No. : 10/031,005
Filed : October 29, 2001
Page : 15 of 15

Attorney's Docket No.: 09531-016002 / 97141

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CONCLUSION

Applicant submits that claims 76, 78, 80-82, 85-103, 106-114, and 116 are in condition for allowance, which action is respectfully requested. The Examiner is invited to telephone the undersigned agent if such would further prosecution.

A Petition for One Month Extension of Time is attached hereto. The Commissioner is authorized to charge \$60 for the Petition for Extension of Time fee, as well as any other charges or credits, to deposit account 06-1050.

Respectfully submitted,

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Elizabeth N. Kaytor
Elizabeth N. Kaytor, Ph.D.
Reg. No. 53,103

Fish & Richardson P.C., P.A.
60 South Sixth Street
Suite 3300
Minneapolis, MN 55402
Telephone: (612) 335-5070
Facsimile: (612) 288-9696

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